CELLULAR AND MOLECULAR IMMUNOLOGY

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Immunity is derived from the Latin word *immunitas,* which referred to the exemption from various civic duties and legal prosecution offered to Roman senators during their tenures in office. Historically, immunity meant protection from disease, and, more specifically, infectious disease. We now know that many of the mechanisms of resistance to infections are also involved in the individual's response to noninfectious foreign substances. Furthermore, mechanisms that normally protect individuals from infections and eliminate foreign substances are themselves capable of causing tissue injury and disease under some situations. Therefore, the modern definition of immunity is a reaction to foreign substances, including microbes, as well as macromolecules such as proteins and polysaccharides, without implying a physiologic or pathologic consequence of such a reaction. Immunology is the study of immunity in this broader sense and of the cellular and molecular events that occur after an organism encounters microbes and other foreign macromolecules. The cells and molecules responsible for immunity constitute the "immune system," and their collective and coordinated responses to the introduction of foreign substances comprise the "immune response."

Historians often credit Thucydides, in Athens during the fifth century B.C., as having first mentioned immunity to an infection that he called "plague" (but that was probably not the bubonic plague we recognize today). The concept of immunity may have existed long before, as suggested by the ancient Chinese custom of making children inhale powders made from the crusts of skin lesions of patients recovering from smallpox. Immunology, in its modern form, is an experimental science, in which explanations of immunologic phenomena are based on experimental observations and the conclusions drawn from them. The evolution of immunology as an experimental discipline has depended on our ability to manipulate the function of the immune system under controlled conditions. Historically, the first clear example of this, and one that remains among the most dramatic ever recorded, was Edward Jenner's successful vaccination against smallpox. Jenner, an English physician, noticed that milkmaids who had recovered from cowpox never contracted the more serious smallpox. Based on this observation, he injected the material from a cowpox pustule into the arm of an 8-year-old boy. When this boy was later intentionally inoculated with smallpox, the disease did not develop. Jenner's landmark treatise on **vaccination** (Latin *vaccus,* cow) was published in 1798. It led to the widespread acceptance of this method for inducing immunity to infectious diseases. An eloquent testament to the importance and progress of immunology was the announcement by the World Health Organization in 1980 that smallpox was the first infectious disease that had been eradicated worldwide by a program of vaccination.

In the last 20 years, there has been a remarkable transformation in our understanding of the immune system and its functions. Advances in cell culture techniques, recombinant deoxyribonucleic acid (DNA) methodology, and protein biochemistry have changed immunology from a largely descriptive science into one in which diverse immune phenomena can be tied together coherently and explained in quite precise structural and biochemical terms. This chapter outlines the general features of immune responses and introduces the concepts that form the cornerstones of modern immunology and that recur throughout the remainder of this book.

NATURAL AND ACQUIRED IMMUNITY

Healthy individuals protect themselves against microbes by means of many different mechanisms. These include physical barriers, phagocytic cells in the blood and tissues, a class of lymphocytes called natural killer (NK) cells, and various blood-borne molecules, all of which participate in defending individuals from a potentially hostile environment. Some of these defense mechanisms are present prior to exposure to infectious microbes or other foreign macromolecules, are not enhanced by such exposures, and do not discriminate among most foreign substances. These are the components of **natural** (also called **native** or **innate**) **immunity.** Other defense mechanisms are induced or stimulated by exposure to foreign substances, are exquisitely specific for distinct macromolecules, and increase in magnitude and defensive capabilities with each successive exposure to a particular macromolecule. These mechanisms constitute **acquired,** or **specific, immunity** (Table 1-1). Foreign substances that induce specific immunity are called **antigens.** By convention, immunology is the study of specific immunity and "immune responses" refer to responses that are specific for different inducing antigens.

The specific immune response is one component of an integrated system of host defense in which numerous cells and molecules function cooperatively.

TABLE 1-1. Features of Natural and Specific (Acquired) Immunity

	Natural	Specific (Acquired)
Physicochemical barriers	Skin, mucous membranes	Cutaneous and mucosal immune systems; antibody in mucosal secretions
Circulating molecules	Complement	Antibodies
Cells	Phagocytes (macrophages, neutrophils), natural killer cells	Lymphocytes
Soluble mediators active on other cells	Macrophage-derived cytokines, e.g., α and β interferons, tumor necrosis factor	Lymphocyte-derived cytokines, e.g., γ interferon

B cell recognition is the finding that T cell responses to a soluble antigen cannot be inhibited using antibodies specific for conformational determinants of that antigen, whereas antigen recognition by B cells can be competitively inhibited by such antibodies.

Role of Accessory Cells in T Cell Responses to Antigens

The second important characteristic of antigen recognition by T lymphocytes is that *T cells recognize and respond to foreign protein antigens only when the antigen is attached to the surfaces of other cells,* whereas B cells and secreted antibodies bind soluble antigens in the circulation or in the aqueous phase. Thus, CTLs recognize antigens bound to the surface of target cells and kill these targets. The activation of helper T cells by foreign antigens requires the participation of cells other than T lymphocytes; these are called **accessory cells.** These accessory cells serve two principal functions in helper T cell stimulation:

1. Accessory cells display fragments of foreign protein antigens on their surfaces in a form that can be specifically recognized by T cell antigen receptors. This phenomenon is called **antigen presentation,** and the cell populations capable of performing this function are **antigen-presenting cells** (APCs). (The term APCs is used for accessory cells that present antigens to helper T lymphocytes. Since CTLs also recognize foreign antigens bound to the surfaces of their target cells, all such target cells may be conceptually included among APCs. Conventionally, however, cells that are recognized and lysed by CTLs are called **target cells,** not APCs.)
2. Accessory cells provide stimuli to the T cell, beyond those initiated by ligand binding to the T cell antigen receptor, which are required for physiologic activation. These stimuli, referred to as **costimulator activities,** are incompletely characterized. They may be provided by membrane-bound or secreted products of accessory cells.

The antigen-presenting functions of accessory cells are described in more detail later in this chapter, and their costimulator functions are discussed in Chapter 7.

The importance of APCs in initiating T cell–dependent immune responses was first suggested in the 1950s by the demonstration that radioactively or fluorescently labeled antigens injected into animals were found in mononuclear phagocytes or follicular dendritic cells and not in lymphocytes. Later studies showed that an antigen that was bound to macrophages *in vitro* and then injected into mice was up to 1000 times more immunogenic on a molar basis than the same antigen administered by itself, in a cell-free form. The explanation for this finding is that T cells respond only to antigen associated with macrophages or other APCs, and only a small fraction of an injected soluble antigen ends up in this immunogenic cell-associated form.

The obligatory role of accessory cells in lymphocyte activation was formally established when techniques for stimulating immune responses *in vitro* were developed. For example, T cells isolated from the blood, spleen, or lymph nodes of individuals immunized with a protein antigen can be restimulated in tissue culture by that antigen. Stimulation may be measured by assaying the production of cytokines by the T cells or by the proliferation of the T cells. When contaminating macrophages and dendritic cells are removed from the cultures, the purified T lymphocytes no longer respond to antigen, and responsiveness can be restored by adding back the macrophages or dendritic cells. Such experimental approaches provide the basis for defining the accessory functions of various cell types in T lymphocyte activation. The importance of accessory cells in immune responses *in vivo* is suggested by the observation that **adjuvants** often need to be administered in addition to antigen in order to elicit an immune response to the antigen. These adjuvants are usually insoluble or undegradable substances that promote nonspecific inflammation, with recruitment of mononuclear phagocytes at the site of immunization.

The Phenomenon of MHC-Restricted Antigen Recognition by T Lymphocytes

The critical advance in our understanding of antigen recognition by helper T cells and CTLs was the discovery of the phenomenon of **self MHC restriction** in the 1970s. *MHC restriction is the requirement that an APC must express MHC molecules that the T cell recognizes as self in order for the T cell to recognize and respond to a foreign protein antigen presented by that APC.* The MHC molecules that T cells recognize as self are those that the T cells encountered during their maturation from precursors in the thymus. (The process of T cell maturation is discussed in much more detail in Chapter 8.) "Self MHC" refers not to MHC molecules expressed by the T cells themselves but to MHC molecules on the APCs or target cells. Normally, because T cells and APCs develop in the same individual, they are syngeneic and all the MHC molecules on the APCs are seen as self MHC by all the T cells in that individual. In experimental systems, T cells respond to antigens presented by a particular APC if the two cell types are at least partly syngeneic, i.e., if they are derived from individuals or inbred strains that share one or more MHC alleles. In this situation the APCs express MHC molecules that the T cells encountered and learned to see as self during their maturation.

This phenomenon of self MHC restriction was discovered when T cells from one inbred strain of animal were mixed with APCs from different inbred strains and T cell responses were assayed. Three sets of ex-